Please amend claim 43 to read as follows:

43. A transformed yeast cell comprising a reporter gene under control of a pheromone-responsive promoter, a heterologous G protein-coupled receptor gene, each said gene being under the control of a separate promoter, a mutation in a SCG1/GPA1 gene, and a hybrid Gα protein, wherein said heterologous G protein-coupled receptor gene does not include a coding sequence from a yeast G protein-coupled receptor gene.

REMARKS

At the outset, Applicants thank Examiner Brannock for the courtesies extended during the telephonic interviews with Eileen Falvey on September 11, 2002 and October 9, 2002. The amendments and remarks made herein reflect the content of those interviews.

Claims 43 to 58 are pending in the instant application. By this amendment, claim 43 has been amended, in order to more particularly point out and distinctly claim the invention. The amended claim 43 is fully supported by the specification and the claims as originally filed. As such, no new matter has been added.

Applicants respectfully request that the amendments and remarks presented herein be entered into the record of the instant application.

I. THE OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

Applicants intend to address this rejection upon an indication that the application is otherwise allowable.

II. THE REJECTION UNDER 35 U.S.C. §103 (a) SHOULD BE WITHDRAWN

Claims 43, 44, 45, 47, 50, 51, 52, 54, 55, 57, and 58 are rejected under 35 U.S.C. § 103 (a) as being obvious over the U.S. Patent No. 5,284,746 issued February 4, 1994 to Sledziewski et al. ("Sledziewski") in view of Kang *et al.*, 1990, Mol. Cell Biol., 10:2582-2590 ("Kang"). According to the Examiner, Sledziewski discloses a transformed yeast cell comprising a reporter gene under control of a pheromone-responsive promoter and a heterologous G-protein coupled receptor gene under a separate promoter, wherein said receptor is a hybrid receptor comprising intracellular sequences from yeast and sequences from

heterologous receptors, wherein said yeast receptor sequences are STE2 sequences, wherein said receptors are capable of inducing yeast pheromone response, and a mutation in the *ste2* gene causes increased sensitivity to receptor activation. According to the Examiner, Kang discloses a heterologous yeast/mammalian hybrid Gα protein expressed in yeast that complements the cell cycle arrest in cells lacking endogenous Gα. According to the Examiner, although Sledziewski does not teach a hybrid Gα protein, it would be obvious to one of ordinary skill in the art, in view of Kang, to use the hybrid G-protein receptors in the Sledjiewski assay.

In response, Applicants submit that the hybrid mammalian G-coupled receptors disclosed by Sledjiewski are not "heterologous" receptors as required by the claimed invention, even according to the definition provided by Stedman's Medical Dictionary cited by the Examiner at page 4, *ll.* 13-16, of the Office Action. A hybrid yeast/mammalian protein is not "normally found" in nature, and is not "derived from an animal of a different species", as required by the dictionary definition of "heterologous." Rather, such hybrid receptors are distinctly artificial, manmade molecules. Therefore, hybrid G-protein coupled receptors should not be considered a subgenus of heterologous mammalian G-protein receptors, the position taken by the Examiner. However, without acquiescing to the propriety of this rejection, in order to facilitate allowance, claim 43, and claims dependent thereon, *i.e.*, claims 44, 45, 47, 50-52, 54, 55, 57 and 58, have been amended to recite a yeast cell comprising a heterologous G protein-coupled receptor ("GPCR") gene which does not include a coding sequence from a yeast GPCR gene. As suggested by the Examiner on page 5 of the Office Action and during the telephonic interview, neither Sledziewski nor Kang, alone or taken together, teach or suggest a yeast cell comprising a heterologous GPCR gene that is not a mammalian/yeast hybrid GPCR gene.

The Examiner contends, however, that such amendment may introduce new issues regarding enablement for the claimed yeast cells. Applicants respectfully disagree. The test for enablement is whether one skilled in the art could make and use the claimed invention, without undue experimentation, from the disclosure coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988). Applicants submit that the specification of the instant application fully enables a yeast cell comprising a heterologous mammalian GPCR that does not include coding sequences from a yeast GPCR fused thereto, for the following reasons.

The instant specification describes and enables a yeast cell which, to achieve efficient heterologous GPCR-mediated signal transduction, comprises, in addition to the heterologous GPCR, *a hybrid Gα protein* which can productively interact with the heterologous GPCR. In fact, the very passage referred to by the Examiner at page 6 of the Office Action, *i.e.*, at page 44 lines 25-30, explicitly states:

> It is conceivable that a foreign receptor which is expressed in yeast will functionally integrate into the yeast membrane, and there interact with the endogenous yeast G protein. More likely, either the receptor will need to be modified (*e.g.*, by replacing its V-VI loop with that of the yeast STE2 or STE3 receptor) *or a compatible G protein should be provided. (Emphasis added.)*

Thus, the heterologous GPCR does not require additional yeast sequences for efficient expression and signal transduction if the alternative solution provided by the instant specification -- modification of the Gα protein to create a hybrid Gα protein that interacts with the heterologous GPCR -- is used.

An example of a yeast cell comprising such a heterologous GPCR and hybrid Gα protein constructed according to the teachings of the instant application as originally filed is provided as Example 10 on page 115, line 28, to page 120, line 14, of the specification.

The Examiner's attention is also directed to the Declaration of Dr. James Broach, with Appendix 1 ("the Broach Declaration"), submitted herewith as Exhibit C. In the Broach Declaration, experimental evidence is presented that clearly demonstrates that heterologous (*i.e.*, human) GPCRs, which lack yeast GPCR sequences, are fully functional in yeast cells comprising hybrid Gα proteins made according to the teachings of the instant specification. In particular, the Broach Declaration presents evidence that a series representative human GPCR genes have been successfully expressed in yeast cells according to the methods described in the instant specification (*See* Table 1 and ¶¶ 4 - 9 of the Broach Declaration).

Attorneys for Applicants submit that the experimental evidence provided by the data in the instant specification and in the Broach Declaration demonstrate that one of ordinary skill in the art would be able to use the teachings of the instant application to make a heterologous mammalian GPCR that does not include coding sequences from a yeast GPCR fused thereto, and use it in the yeast cell screening assays, as described and claimed in the instant application, without undue experimentation.

For all the reasons presented above, the claims, as amended, are fully enabled under 35 U.S.C. § 112, first paragraph.

CONCLUSIONS

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the instant patent application. Applicants believe that the foregoing amendments and/or remarks made herein now place the pending claims in condition for allowance. The Examiner is invited to contact the undersigned with any questions concerning the foregoing.

Respectfully submitted,

Date: January 3, 2002

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Enclosures

EXHIBIT A

MARKED-UP AMENDMENTS TO THE CLAIM
(with additions indicated by underlining)

WHAT IS CLAIMED IS:

43. (amended) A transformed yeast cell comprising a reporter gene under control of a pheromone-responsive promoter, a heterologous G protein-coupled receptor gene, each said gene being under the control of a separate promoter, a mutation in a SCG1/GPA1 gene, and a hybrid Gα protein, wherein said heterologous G protein-coupled receptor gene does not include a coding sequence from a yeast G protein-coupled receptor gene.